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REVIEW

Lasers: Reflections on Their Evolution

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A review of the past 22 years of laser applications shows that a great deal of progress has been made. It allows one to see the evolution of laser therapy, compare it with other modalities used in surgical oncology, and identify certain program that merit clinical trial.

Use of lasers in surgical oncology began with a laser knife. Tissues were divided and removed with the focused beam of the CO_2 laser, which replaced the scalpel previously used to perform surgical procedures. Later, the Nd:YAG laser was used in hollow visci such as the trachea and esophagus to open obstructed passages and possibly to cure many cancers. The operating microscope was used in the larynx to remove benign and malignant lesions, and for obstructing lesions to provide time to treat medical complications by reopening airway passages, and to add irradiation and/or chemotherapy preoperatively. Many times the Nd:YAG laser was used gastroscopically to treat bleeding or obstruction. Cytoreduction by laser made surgery or chemotherapy, or both, plausible. Addition of the sapphire tip and, later, the bare or sculptured fiber increased the variety of procedures possible with the Nd:YAG laser.

Photodynamic therapy (PDT) uses various drugs that are localized in cancer cells. The cancer is then destroyed by laser emissions of the proper wavelength. One of the problems with PDT is getting the light to the tumor. Preactivation is addressed in this report. The problems associated with anaerobic tumors are discussed and suggestions for clinical trials offered.

Laser hyperthermia is compared with induced hyperthermia as well as in combination with irradiation. Protocols of local laser hyperthermia combined with irradiation need further exploration.

This review addresses the use of lasers in the destruction of tumor cells for bone marrow transplant and several old and new experiments used to block the AIDS virus. Finally, ongoing research is discussed, including the present and future roles of lasers. **J. Surg. Oncol. 64:84–92**

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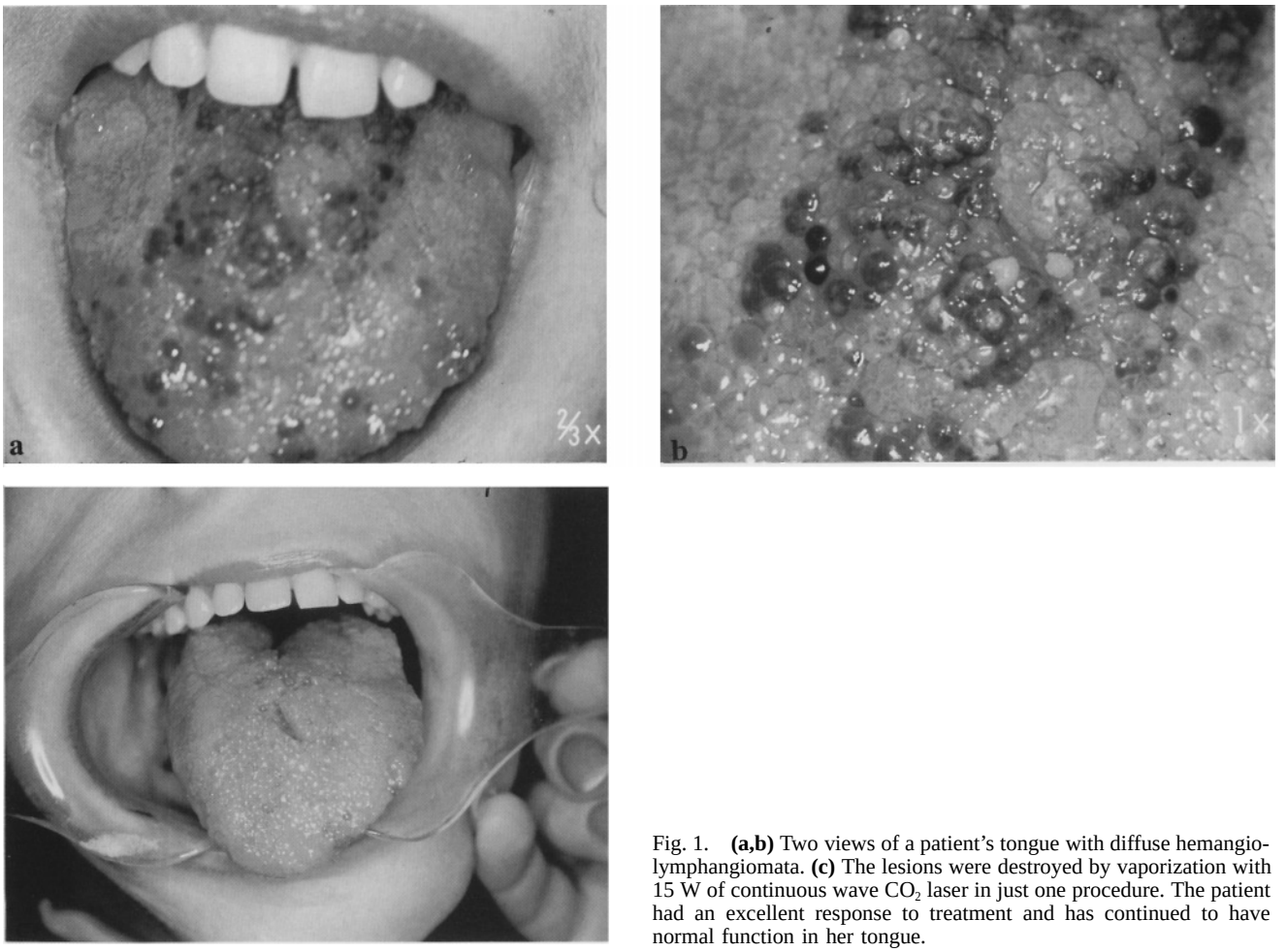


Fig. 1. **(a,b)** Two views of a patient's tongue with diffuse hemangiolymphangiomata. **(c)** The lesions were destroyed by vaporization with 15 W of continuous wave CO_2 laser in just one procedure. The patient had an excellent response to treatment and has continued to have normal function in her tongue.

HISTORY OF LASER DEVELOPMENT

Research by Albert Einstein and later by Schawlow and Townes [1] at Bell Laboratories led to the description of the laser in 1957. Ted Maiman [2] built the first ruby laser in 1960, and Patel built the first CO_2 laser in 1964. In 1972, Sharon and Kaplan completed one of the first usable surgical lasers, which offered great potential. The first CO_2 laser did not have a directional beam, but the next year a HeN_2 laser pointer was added. Development of other lasers, such as the argon and neodymium-yttrium-aluminum-garnet (Nd:YAG) lasers, soon followed. Interstitial laser therapy was developed using the Nd:YAG for tumors of the oesophagus, tracheobronchial tree, and other internal organs.

Various changes in the Nd:YAG delivery system allowed treatment of smaller areas with less lateral tissue destruction. Photodynamic therapy progressed with the development of a tunable dye laser and the availability of photodynamic drugs such as hematoporphyrin.

The free electron laser, developed as part of the Star Wars program, has both medical and surgical applications. As lasers continued to mature, they were combined with other lasers, interstitial laser therapy (ILT) [3], Cavitron ultrasonic surgical aspiration (CUSA), chemotherapeutic drugs [4], and other modalities to extend the limits of palliation and cure.

Initially, a CO_2 laser with ~35 W of power was used. It had a focal point of 0.3 mm and a flexible arm that improved access to many areas. The laser had some hemostatic properties and, more importantly, blocked lymphatics. One could operate on fibrotic-irradiated areas or even freshly treated areas. The hemostasis was excellent. Healing was satisfactory, particularly if subcutaneous closure or minimal skin sutures were placed.

The CO_2 laser has had numerous other applications. The laser is frequently used in head and neck surgery, and it is well suited for dissections of the neck, tongue, lip, and cheek. In the treatment of breast cancer, however, results are similar to those achieved with the scalpel.

For years, the Nd:YAG laser has been an excellent instrument for the treatment of bronchial, esophageal, and colonic tumors. The laser's flexible fiber makes reaching and palliating the tumor possible. Modification of the

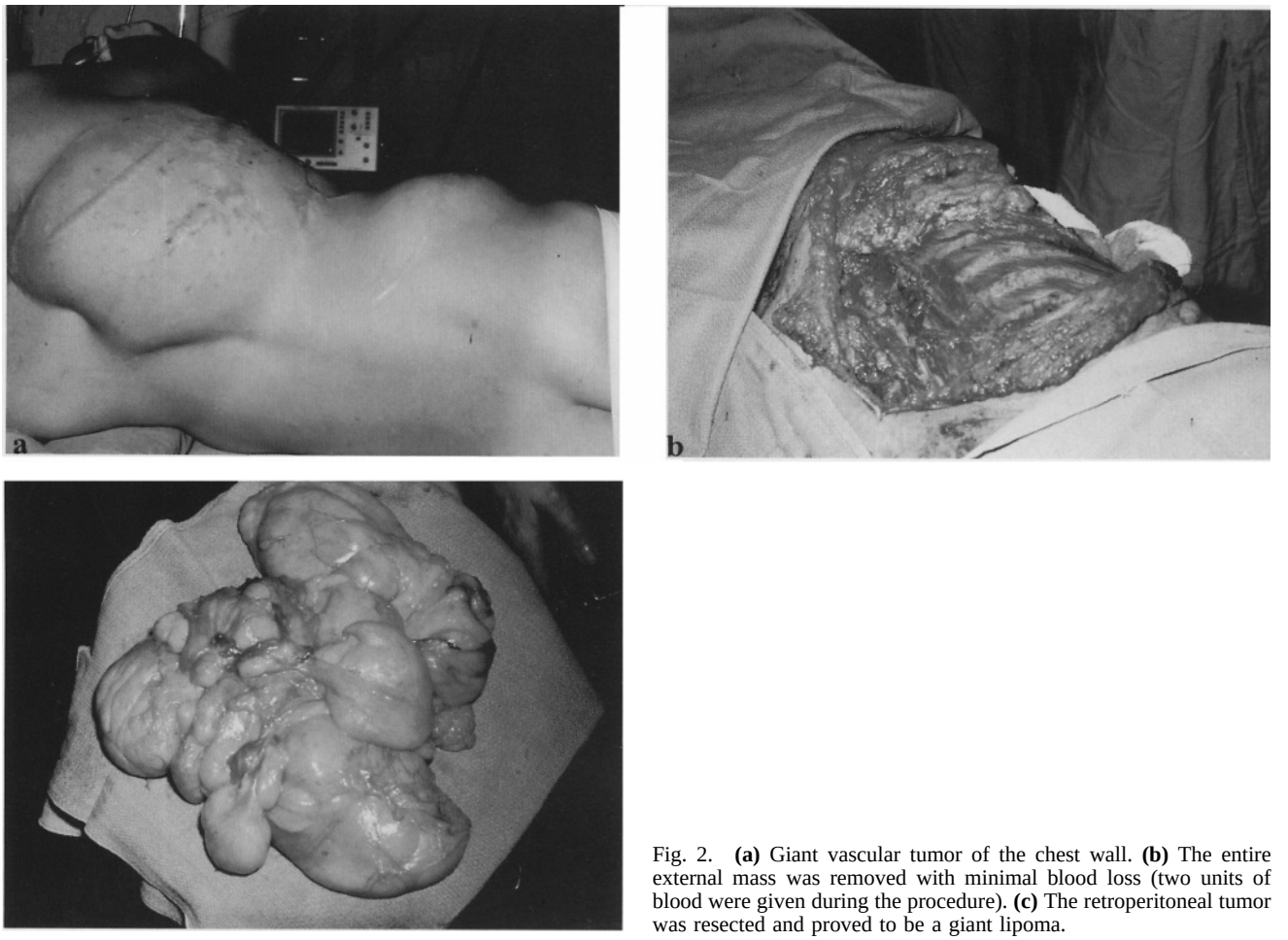


Fig. 2. **(a)** Giant vascular tumor of the chest wall. **(b)** The entire external mass was removed with minimal blood loss (two units of blood were given during the procedure). **(c)** The retroperitoneal tumor was resected and proved to be a giant lipoma.

Nd:YAG with sapphire tips or bare or sculptured fibers extends these parameters [4]. Photodynamic therapy, which has extended laser use, is reviewed later in this discussion.

Many vascular anomalies have been easily destroyed or removed with minimal, if any, scarring or pain. A case in point was a young patient who had diffuse hemangiolymphangiomata of the tongue (Figs. 1a,b) with chronic recurrent infections and hemorrhage, at times requiring hospitalization. The entire tongue was treated by the author in one procedure by vaporizing the vascular lesions covering the surface. The patient responded well to treatment and went home the next day (Fig. 1c). Giant vascular tumors of the chest wall and abdomen were removed (Fig. 2a,b) in a patient who had undergone 11 previous operations. Later, the retroperitoneal tumor was resected and proved to be a giant lipoma (Fig. 2c). Three years later, the patient developed a hemangioma of the liver. She refused surgery with the laser, but was successfully treated by embolism of the vascular tumor in the liver. A long-term follow-up showed cure.

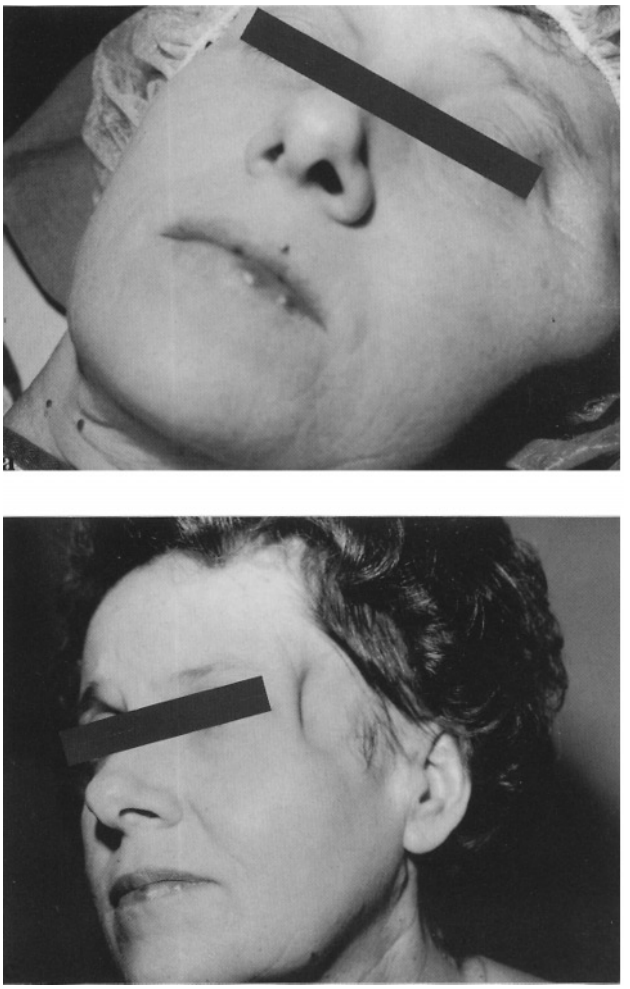
Several cases of idiopathic thrombocytopenia were treated. In one patient, a previously attempted resection of the temporal mass (Fig. 3a,b) resulted in removal of the zygomatic arch and in massive hemorrhage. Later, the patient was treated with cortisone and eventually had a splenectomy. Resection of the tumor with CO_2 laser was successful (Fig. 3c), with minimal blood loss. The patient has remained well and has normal platelet counts.

Laser resections of the lobes of the liver and small tumors of the liver were accomplished with decreased blood loss. A "combo" laser was developed that combined simultaneous CO_2 and Nd:YAG beams. The wattage was additive and seemed to work well in animals. FDA approval came too late in this surgeon's career.

INTRA-ARTERIAL OXYGEN

For many years, surgical procedures were combined with x-ray therapy and chemotherapy, and many protocols were developed. During the early years, the cellular effects of irradiation therapy were heavily debated by radiologists. Today, we have a better understanding of these effects.

Ionizing radiation has the following effects on oxygen in water: (1) irradiation of water in an *oxygen-free* environment results in H^+ and OH^- radicals (half-lives are



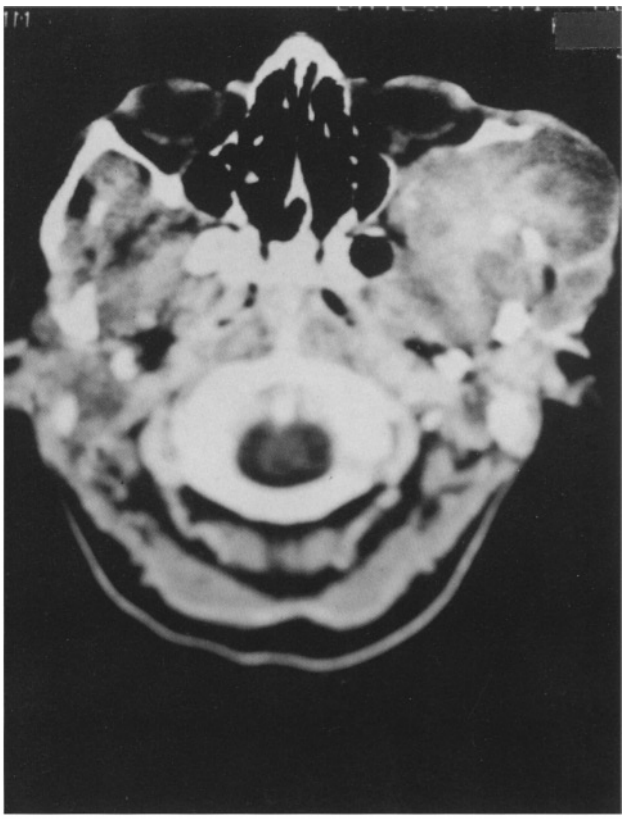


Fig. 3. **(a)** Patient with idiopathic thrombocytopenia. **(b)** CT scan shows the extent of the tumor. **(c)** Resection of the tumor with CO_2 laser was successful, with minimal blood loss.

10^{-13} sec), which can recombine to form water, (2) irradiation of water in an *oxygen-rich* environment results in O_2H (perhydroxyl), H^+, and OH^- radicals. In the oxygen-rich environment, the hydrogen ion combines readily with oxygen to form the highly reactive perhydroxyl radical (the OH^- and O_2H radicals survive much longer). In a biological system, the perhydroxyl radical oxidates sulfhydryl groups ($\frac{S}{H} = \frac{S}{H}$) in compounds such as cysteine-cysteine and other amino acids in DNA and RNA. Breaking these chains results in cell death. Therefore, 90% of the killing power of ionizing radiation is in the production of reactive free radicals (e.g., *hypoxemia* results in irradiation protection, whereas *hyperoxemia* [or nascent O_2] results in increased irradiation-induced cell death) (pers. corres.: James W. Finney, Pain Treatment Center, Forth Worth, TX, March 19, 1996).

We developed a technique for using intra-arterial O_2 combined with ionizing irradiation, chemotherapy [6], and even antibiotic treatment. Early in the 1960's, we used this technique to treat head and neck tumors. First, a catheter was inserted into a branch of the external carotid artery. If a subsequent neck dissection were to be done, we insisted on a retrograde introduction into the superficial temporal artery. The vessel was exposed and a 5 French polyvinyl catheter was introduced retrograde into the vessel. We usually used fluorescein to assure florescence of the tumor area. The catheter was anchored, and the upper end of the catheter was placed subcutaneously to exit above or behind the ear [7]. The catheter was heat-sealed and cut to open at the time of treatment. Oxygen was obtained from a mixture of hydrogen peroxide (Abbott Laboratories, Chicago, IL) and 250 cm^3 of Ionosol T (Abbott Laboratories) in 5% dextrose with 25 or 50 mg of tolazoline (Priscoline, Ciba-Geigy, Summit, NJ). Then 5–40 cm^3 of 3% pharmaceutical grade hydrogen peroxide was added. The resultant concentration was 0.06% to 0.48% peroxide solution. This solution was placed in an infusion bag and forced in slowly, under pressure. When tolerated well, the solution was given at a rate of 5–10 cm^3 per min. Irradiation was given while infusion was in progress. When completed, the catheter was flushed with concentrated heparin (10,000 μ/cm^3) and sealed with heat [8].

The results were quite amazing. Smaller x-ray doses gave very rapid destruction of the tumor, and the recovery (healing) of the lesions was rapid. One of the early cases of

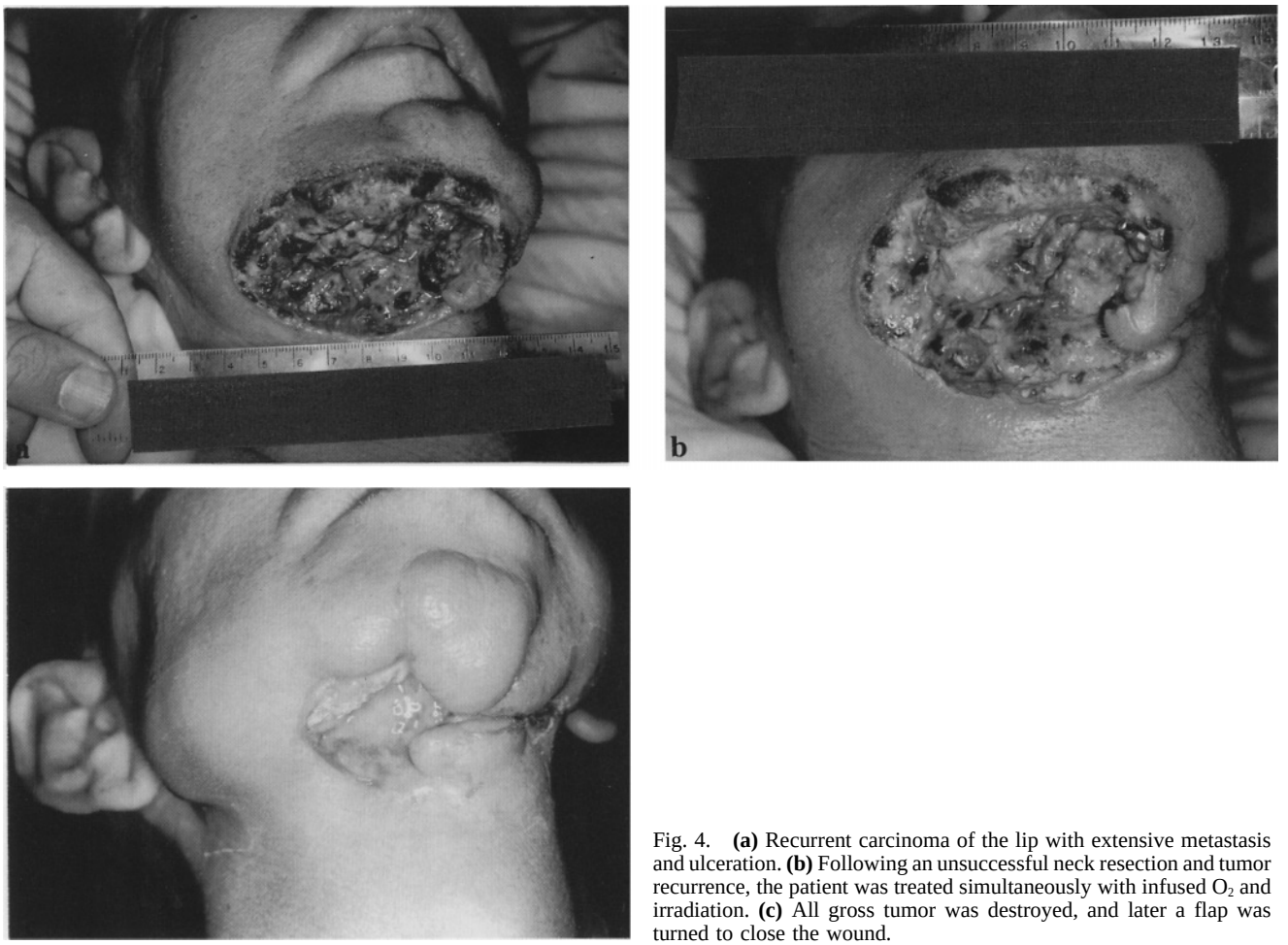


Fig. 4. **(a)** Recurrent carcinoma of the lip with extensive metastasis and ulceration. **(b)** Following an unsuccessful neck resection and tumor recurrence, the patient was treated simultaneously with infused O_2 and irradiation. **(c)** All gross tumor was destroyed, and later a flap was turned to close the wound.

tumor recurrence is shown in Figure 4a. Previous surgical treatment, including a neck resection with a mandibulectomy and placement of a metal prosthesis, was unsuccessful. The tumor recurred and the patient was treated by inserting a catheter into the external carotid and infusing peroxide simultaneously with irradiation. The patient received a total of 4,000 cGy (Fig. 4b). All gross tumor was destroyed (Fig. 4c), and eventually a flap was turned to close the wound.

A later case, a large lesion involving the entire lower lip (Fig. 5a), was treated using a mask to divide the tumor into three areas (Fig. 5b). Irradiation treatment was given before, during, or after peroxide (O_2) infusion. After receiving 2,400 cGy, the area treated with irradiation *during* the peroxide infusion showed healing following tumor destruction; the areas receiving 4,000 cGy *before* or *after* infusion showed a much slower effect. However, the tumor recurred in the area receiving less irradiation (2,400 cGy) simultaneously with peroxide infusion. This experience taught us that despite the rapid regression of tumors, it was necessary to give the usual cGy to obtain cure.

Photodynamic therapy appears to be related to ionizing irradiation therapy because the action on oxygen is similar. Photofrin® (porfimer sodium, QLT Phototherapeutics, Seattle, WA) is selectively retained by tumor cells. Cellular damage occurs when porfimer sodium is activated by the proper wavelength of laser light (630 nm). Energy transfer from porfimer sodium to molecular oxygen generates singlet oxygen, resulting in the subsequent formation of superoxide and hydroxyl radicals that destroy tumor cells. Tumor death also may occur through tumor necrosis and vascular occlusion that seems to be partially mediated by thromboxane A_2 release. The laser treatment induces a photochemical rather than a thermal effect [9,10].

Figure 6a shows a head and neck tumor that was marginally operable due to the patient's age (84 years) and severe chronic obstructive pulmonary disease. The patient was first given 25 mg/kg intravenous hematoporphyrin derivative (HpD_2). Three days later, the patient received an initial treatment with 630 nm argon-pumped dye laser, which was repeated on day 5. There was marked regression of the tumor at 4 weeks (Fig. 6b), with complete destruction of the tumor at 8 weeks (Fig. 6c). There was no recurrence for 4 years, at which time follow-up was discontinued.

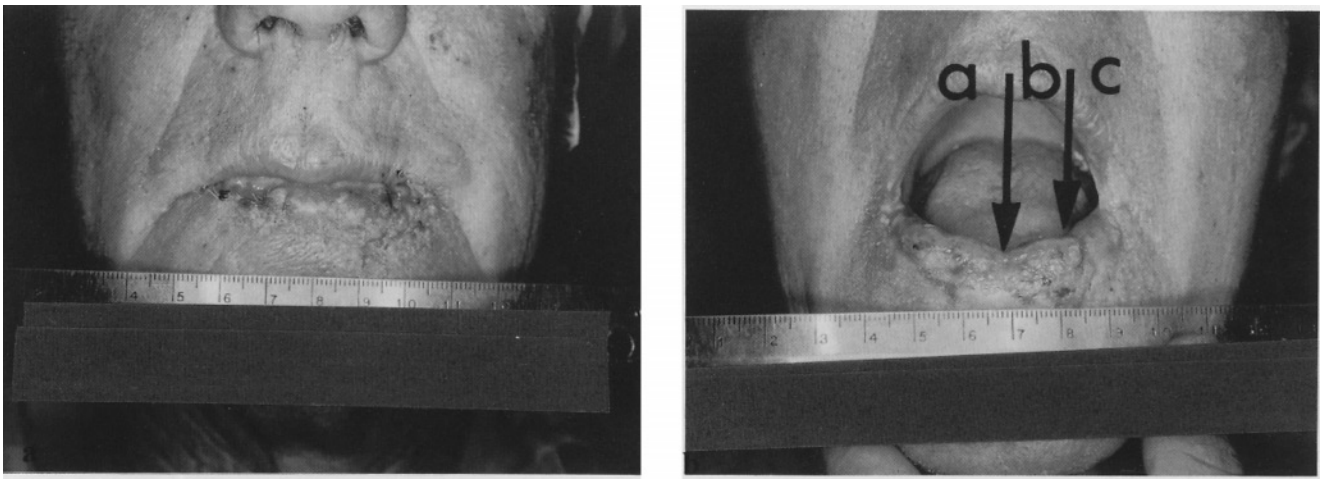


Fig. 5. **(a)** A large lesion occupying most of the lower lip. **(b)** The tumor was divided into three treatment areas using a mask: *area a* was irradiated prior to peroxide infusion: *area b* was irradiated 30 minutes after peroxide infusion; *area c* was irradiated simultaneously with peroxide infusion. Areas a and b received 4,000 cGy; area c received 2,400 cGy (note the mucosal covering in area c). There was recurrence in area c.

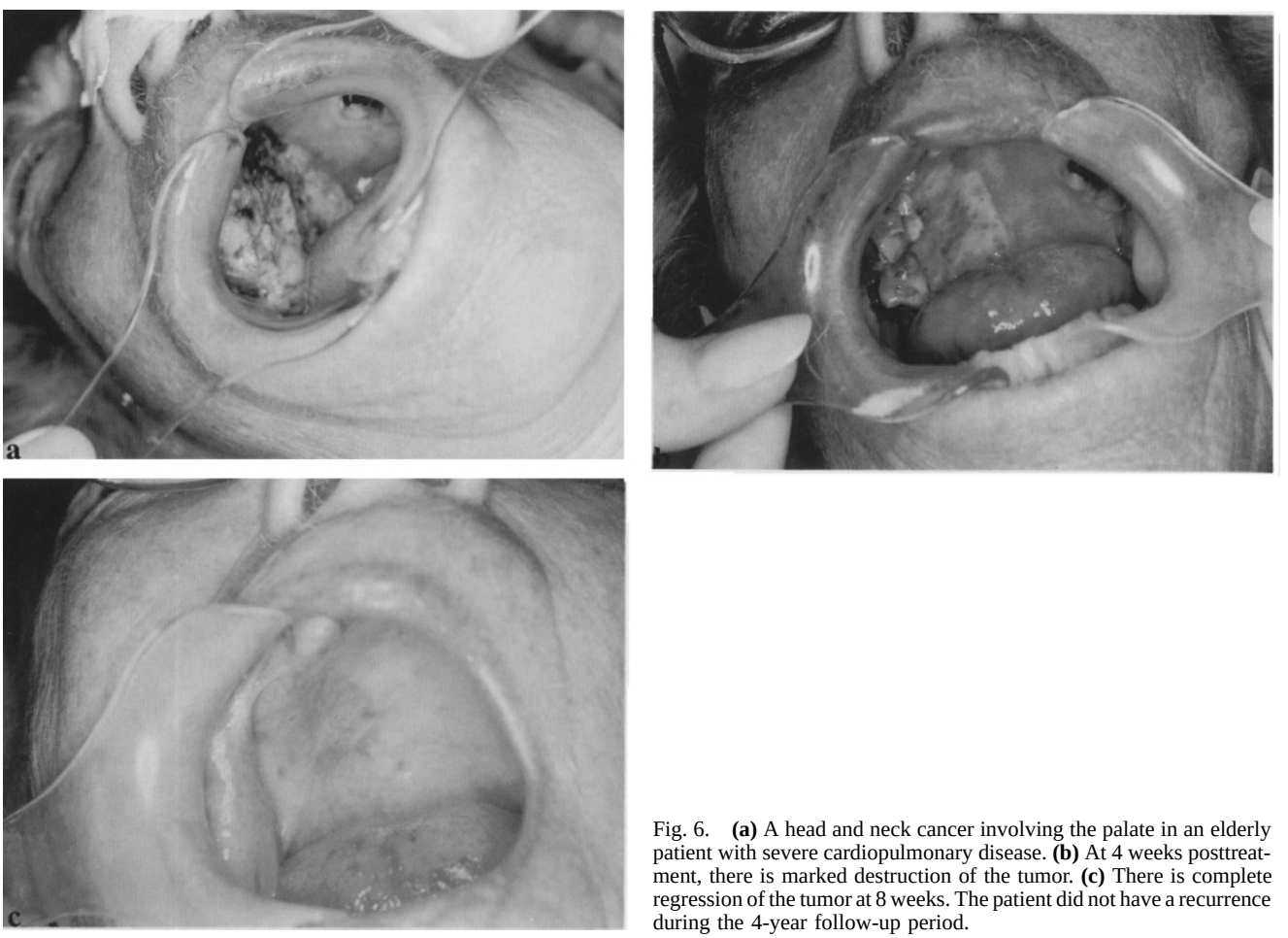


Fig. 6. **(a)** A head and neck cancer involving the palate in an elderly patient with severe cardiopulmonary disease. **(b)** At 4 weeks posttreatment, there is marked destruction of the tumor. **(c)** There is complete regression of the tumor at 8 weeks. The patient did not have a recurrence during the 4-year follow-up period.

Photodynamic therapy has several problems. A major complaint is photosensitivity of the patient from 30 to 100 days. Working with Chinese herbs and white rabbits, we found that the animals could be protected from ultraviolet light. We noticed a marked diuresis and decided to try PDT in conjunction with diuretic therapy (Aronoff BL,

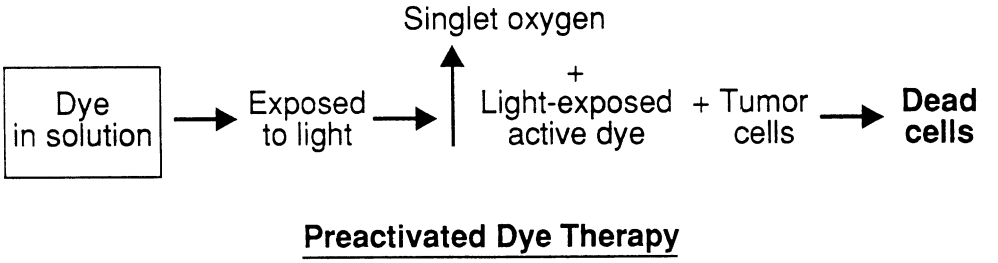


Fig. 7. Preactivated therapy: Energy transfer from porfimer sodium to molecular oxygen generates singlet oxygen, resulting in the subsequent formation of superoxide and hydroxyl radicals that destroy tumor cells.

Chen Z-Y: Application of traditional Chinese medicine to decrease some sensitivity to hematoporphyrin derivative, unpub. obs.). We were careful to complete the PDT and then start Diuril (chlorothiazide). We found that in less than a week, most patients had lost their sun sensitivity. We also found that many of our PDT failures were patients taking the diuretic before and during treatment. A patient who had a morphea basal cell that was treated successfully was still sun-sensitive for 105 days. A year later, she developed another lesion and was treated with HpD and PDT. Following treatment, she was placed on chlorothaizide and her sun sensitivity was cut to 8 days.

Another problem is achieving laser light to cause tumor death. We are studying preactivation of photoactive compounds in which the active agent is no longer dependent on illumination at the target site and can be carried to the tumor in a manner similar to other chemotherapeutic agents. This preactivation procedure requires less laser light and decreases photosensitivity (Fig. 7). We are well into this study, which is being conducted by Dr. Kirpal Gulliya [11].

There are other problems, the greatest of which is anoxia of the tumor cells. A great deal of research is underway to identify new drugs that will react with low O_2 concentrations. Our contention is that regional oxygenation concomitant with PDT should be studied using current and newly developed drugs. The amazing results with oxygen and irradiation demand clinical trials.

HYPERTHERMIA

In their excellent article, Masters and Bown [12] review hyperthermia with interstitially placed laser fibers: interstitial laser hyperthermia (ILH). This relatively new technique is compared with intraoperative attempts and the percutaneous, guided-magnetic resonance imaging (MRI) and computed tomography (CT) needle placement. Masters and Bown use low-power (1–3 W) Nd:YAG therapy at 200–1,000 second exposure. All placements are checked, and the treatments are monitored by real-time ultrasound. The treated tumors undergo gradual transition from an initial mixed echogenic pattern to a final, hyperechogenic pattern by the end of treatment. For larger tumors, the transformation allowed clear delineation between treated and untreated areas. Preoperative, guided-needle biopsies were used for diagnosis and were repeated posttreatment to evaluate the results. Requirements for treatment of liver metastases include a positive biopsy, no extrahepatic spread, and less than four hepatic deposits (none exceeding 6 cm in diameter). Masters and Bown treated 10 patients with a total of 18 metastases (mean diameter 3 cm). The treatment was repeated on 31 occasions using a 1×4, 200 μm-fiber coupler. Up to four hollow 19-gauge needles (external diameter 0.8 mm) were placed. The 200-μm fiber was inserted through the needle so that a length of 2–3 mm of bare fiber penetrated beyond the needle into the tumor. The laser was operated between 1.5 and 2.0 W for at least 500 seconds. Masters and Bown included a 1 cm rim of sonographically normal liver around the metastasis. These needles were changed to encompass the entire tumor; the ultrasound changed from a mixed echogenic pattern to a hyperechogenic appearance.

At 24-hour and 1–2-month intervals, a contrast-enhanced CT scan and needle biopsy were performed. Later follow-up revealed normal liver architecture with extensive adjacent fibrosis. Similar results were found following treatment of breast tumors, some of which were excised within a week. Studies of tumors of the pancreas, colon, and stomach identified the need for further studies.

The use of hyperthermia in cancer treatment dates back to ancient medicine and the application of red-hot irons by Ramajama (2000 BC), Hippocrates (400 BC), and Galen (200 AD). In more recent times, Westermark (1898) placed hot-water circulating cisterns into advanced carcinomas of the uterus. Coley (1927) introduced "toxin" therapy to elevate the body temperature for cancer treatment. Warren (1933) was one of the first to use infrared and high-frequency currents to treat tumors. Little more was done until the late 1970s [13].

Cancer cells at temperatures of 41–45°C are more sensitive than their noncancerous counterparts. More damage can be obtained with a slightly higher temperature of longer duration. Hyperthermia produces many changes, including the alteration of both DNA and RNA synthesis

and the depression of cellular enzymatic synthesis [14,15].

Hyperthermia may be produced by fluid immersions in a tank or specially constructed space suit; irrigation, regional perfusion with heated fluids; and by electromagnetic, radio-frequency waves. Heating is limited with commercial diathermy equipment (range of 915–2450 MHz microwave bands). Even with surface-cooling, documented temperatures of 42–44°C have been possible at 2–3 cm depths, with a thermal gradient decrease with depth. Isolated-limb perfusion has been accomplished with prewarmed blood at 41.5–43.5°C, with good results but high complication rates. Total body hyperthermia at 41.8°C for an average of 4 hours was achieved using molten wax; some deaths from internal vascular coagulation resulted. Total body hyperthermia at 41.5–42°C for 4 hours also was achieved using a water-circulation suit; one death was reported, as well as cardiac arrhythmias, superficial burns, and transient respiratory distress [13,16].

THERMORADIOGRAPHY

Thermoradiography [17], a combination of hyperthermia and radiotherapy, has produced a synergistic and augmented response. Many theories about the effects of hyperthermia have been advanced. One theory suggests that thermoradiography inhibits cellular recovery from sublethal radiation damage. The amount of cell damage has been demonstrated in the laboratory. The Radiation Therapy Oncology Group has established clinical trials using a thermal range of 43–45°C plus 4,000 cGy over 4 weeks [18–24].

The greatest problem lies in achieving adequate localized heat. It would seem that a combination of laser-induced thermotherapy and irradiation of the tumor by the usual modalities would prevent total body or extremity heating, and adequate irradiation could be obtained. However, there is no evidence of this type of trial. Castro et al. [3] discusses MRI-guided, interstitial laser phototherapy. Three-dimensional thermal mapping with direct display of heat distribution and excellent tissue delineation in hyperthermia confirm the effectiveness of treatment.

LASER RESEARCH

In our laboratory at Baylor Research Institute, we have studied a light irradiation system form of inactivation of the enveloped viruses (e.g., HIV). In this system, banked blood is mixed with HpD and circulated through a series of transparent coiled tubes. This blood is circulated through a flow-cell in front of proper wavelength (630 nm) light and collected in a sterile container. This light inactivates the virus by altering its outer coat.

Another project involves photochemicals, which can be activated with visible light, to cross-link proteins. Because some proteins associated with the membranes of cells have to change their structural configuration to serve their function, cross-linking these proteins blocks their function. A classic example of this protein phenomenon is the CD_4 receptor on lymphocytes susceptible to the AIDS virus. For the virus to invade the cell, proteins associated with the CD_4 receptor must change their configuration. Cross-linking proteins with the light-activated dyes blocks the infectivity of the virus. Viruses are also directly inactivated by linking the proteins via their membranes with photochemicals.

Bone marrow purging is another project we are studying. Usual purging methods, including irradiation, destroy a high percentage of tumor cells as well as stem cells, thus affecting the results of bone marrow transplants. In a new procedure, bone marrow is obtained, treated with merocyanine 540 (MC540), and irradiated with the laser. This procedure destroys most of the tumor cells while destroying only a small percentage of stem cells. The MC 540 is rinsed off and the bone marrow is then given to the patient.

LASER PHOTOCHEMOTHERAPY

Laser photochemotherapy combines photodynamic and photothermal interaction with chemotherapeutic drugs to treat cancer. The recent developments of open MRI and color Doppler ultrasound (UTZ) allow accurate, noninvasive monitoring during resection or thermal ablation via laser fiber-optics. Localized hyperthermia can be delivered interstitially by various energy sources, such as focused, high-intensity ultrasound, radio frequencies, microwaves, or lasers.

Photochemical activation of anthracyclines has been demonstrated with daunomycin and Adriamycin (doxorubicin) [4]. Formation of excited states of these drugs and generation of radical oxygen species are wavelength dependent (313–498 nm). Doxorubicin derivatives are the most common anticancer agents that interact with light to elicit fluorescence, membrane-photolabeling, laser activation, and killing of tumor cells. Daunomycin localizes in the cell cytoplasm and binds to tumor cell membranes at a significantly greater level than doxorubicin, which localizes in the nucleus. The toxicity of daunomycin is increased by argon light [4].

Photochemosurgery with lasers offers a new alternative therapy, consisting of monochromatic light delivered via external or interstitial fiber optics to enhance the “killing” threshold in tumor cells that contain light-sensitive anthracycline derivatives. This technique offers specific advantages, including a maximum 1-cm limit of light penetration from the fiberoptic tip.

CONCLUSIONS

An attempt has been made to follow the maturation of the laser. The laser has been combined with many modalities and has even greater potential. Ionizing irradiation combined with interstitial laser therapy for heat could

demonstrate the combined synergistic effect and improve the cure or palliation of tumors. The similarities of therapeutic irradiation and PDT are striking. The combination of intra-arterial O_2 with PDT should improve results, allow decreased drug doses, and prevent related side effects.

Close collaboration between experimental laboratory and clinical applications should improve methods of treatment. Lasers are still in their infancy and must continue to mature.

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